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Hydrogen's isotopic exchange reaction in the C-methyl sides in the medicinal agent xymedon: NMR spectroscopy and ab initio calculations

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Abstract

Copyright © 2018 John Wiley & Sons, Ltd. The kinetics of intramolecular and intermolecular exchange processes in xymedon (1-(2-hydroxyethyl)-4,6-dimethyl-1,2-dihydropyrimidin-2-one, a regeneratory, wound-healing drug) and its analogue were investigated in the solution. Hydrogen's mobility was detected in the C-methyl sides of these compounds. This mobility was monitored via NMR in the hydrogen/deuterium exchange reaction in water. Two models were proposed as explanations for this hydrogen-deuterium exchange. According to the main model, the key intermediates of these reactions are low-energy tautomers of xymedon in which the N3 is protonated following which one proton leaves either 6-Me or 4-Me and thus its hybridization is changed. This hydrogen-to-deuterium exchange reaction is much faster under acidic conditions although it also occurs in alkaline conditions. Methylation via MeOTs or MeI leads to products with a quaternized ring N3 atom in which a hydrogen-to-deuterium exchange reaction also takes place, although the rates of the 6-Me and 4-Me hydrogens exchange are reversed. According to density functional theory calculations, the presence of methyl groups at the C4/C6 positions and of the C=O fragment is crucial to remarkably lower the energies of these “rare” tautomers. The exact position of the C=O in heterocycle is also very important in the tautomers' relative stability.

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